Seasonal changes in mood and behaviour in the general population

Associations with mood, sleep and health risk factors

Nicolas Melchior Frederic Øyane

Dissertation for the degree philosophiae doctor (PhD)

at the University of Bergen

2010

Scientific environment

This work was carried out at the Department of Public Health and Primary Health Care, University of Bergen, Norway and Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital, Bergen during the period 2004-2010. The work is based upon data from the Hordaland Health Study (HUSK), a health survey carried out in 1997-99 by the National Health Screening Service, the University of Bergen and local health services.

The PhD-candidate was granted admission and has followed doctoral training and PhD-courses at the Faculty of Medicine, University of Bergen.

Section of General Practice,

Department of Public Health and Primary Health Care, University of Bergen, Norway

Norwegian Competence Center for Sleep Disorders,

Haukeland University Hospital, Bergen, Norway

Acknowledgements

First of all, I would like to thank the thousands of inhabitants in Hordaland County participating in the Hordaland Health Study (HUSK). They have all contributed to an invaluable dataset for researchers in medical epidemiology. Additionally, many thanks goes to the National Health Screening Service, the University of Bergen and local health services for having organized this incredible health survey.

I would also like to thank my supervisor Bjørn Bjorvatn for his priceless guidance and support throughout these years. He has without doubt been my most important research partner and helped med to grasp the fascinating world of medical research. He has learnt me most of what I currently know about data analyses, manuscript writing and revisions. I also thank him for his excellence in research, his everlasting optimism and extraordinary ability to motivate even when things are going slow. I truly can not think of anything more one could wish from a supervisor.

Reidun Ursin, Ståle Pallesen, Ingvar Bjelland and Fred Holsten were co-authors on one or more of my papers, and I would like to thank them all for a significant contribution to my work. A special thank goes to Ståle Pallesen for patiently and skilfully being my guru in epidemiological statistics.

Many thanks to the stimulating and motivating environment of the National Competence Center for Sleep Disorders (SOVno), where I have received grants to present abstracts at different congresses around the world. Also thanks to the research milieu at the Institute of Department of Public Health and Primary Health Care at the University of Bergen.

Finally, I believe that a high motivation for research is highly dependent on motivating and vital activities outside the research environment. Therefore, I would like to give many thanks my friends, my family and especially my wife Silje for their precious support throughout these years.

Abbreviations

ANOVA: Analysis of variance

BMI: Body Mass Index

CI: Confidence Interval

DSM IV: Diagnostic and Statistic Manual of Mental Disorders, Fourth Version

GSS: Global Seasonality Score

HADS: Hospital Anxiety and Depression Scale

HADS-A: Anxiety subscale of HADS

HADS-D: Depression subscale of HADS

SAD: Seasonal Affective Disorder

s-SAD: Subsyndromal SAD

SPAQ: Seasonal Pattern Assessment Questionnaire

Definitions

Confounder is an extraneous variable in a statistical model that correlates (positively or negatively) with both the dependent variable and the independent variable.

Hyperphagia is a medical sign meaning excessive hunger and abnormally large intake of solids by mouth.

Hypersomnia is characterized by recurring episodes of excessive daytime sleepiness or prolonged sleep duration. Subjects with hypersomnia usually need to nap repeatedly during the day.

Insomnia is a sleep disorder with a perception of inadequate or poor-quality sleep due to difficulty falling asleep, nightly awakenings, waking up too early in the morning or unrefreshing sleep. The diagnosis requires subjects to experience daytime consequences related to their sleep difficulties.

Observation or information bias results from systematic differences in the way data on exposure or outcome are obtained from the various study groups.

Seasonality is usually referring to seasonal variations of any measurable phenomenon, nevertheless, we here constraint the definition to variations in mood and behaviour in humans by seasons.

Seasonal Affective Disorder (SAD) is an affective disorder characterized by recurrent depression during a certain time of the year, with full remission during another time of the year. Subjects should experience at least one recurrence, and the depression should be severe enough to qualify the criteria for major depressive episode according to DSM-IV.

Selection bias can occur whenever the identification of individual subjects for inclusion into the study depends in some way on the outcome measures.

Subsyndromal SAD is a less severe type of SAD, where subjects do not fullfil the diagnostic criteria for a major depressive episode.

Winter-SAD is the most common form of SAD, where the depressive episodes occur during winter.

Summer-SAD is a less common variety, where the depressive episodes occur during summer.

Abstract

The way seasons affect humans varies considerably between individuals, nevertheless most humans' mood and behaviour change throughout the year. Almost 25 years ago, Seasonal Affective Disorder was described as recurring major depressive episodes during a certain time of the year. Seasonal Affective Disorder has been reported to be associated with hypersomnia, increased appetite and carbohydrate craving, and the disorder is most common in subjects with high education and socioeconomic status. However, some subjects report a high degree of seasonal changes in mood and behaviour (seasonality) without fulfilling diagnostic criteria for depression. The aim of this thesis was to characterize these subjects with respect to demographic factors, anxiety, depression, sleep and general health risk factors. We analyzed data from a large health survey, the Hordaland Health Study (HUSK). Invitation letters were sent to all men and women aged 40-44 years in Hordaland County, Norway (n=29.400), and the attendance rates were 57% among men and 70% among women. Subjects were asked to fill in the Global Seasonality Score Questionnaire, measuring seasonality on a 6-item scale. Additionally, they completed questionnaires on demographic characteristics, general health, anxiety/depression and sleep. They underwent an examination where weight, height, waist/hip circumference, blood pressure, blood glucose and blood lipid levels were measured. We found high degree of seasonality to be associated with female gender, low educational level, low annual income and being single. Furthermore, high seasonality per se was significantly correlated to anxiety, depression and sleep problems (mainly associated with

insomnia). Subjects with high seasonality also had more health risk factors than subjects with low seasonality. In conclusion, high seasonality did not share the same characteristics as seasonal affective disorder, and seasonality in itself could be a risk factor for both anxiety and depression. Our results could therefore justify seasonality to be a separate dimensional trait associated with several diseases, including depression.

List of publications

Oyane NM, Holsten F, Ursin R, Pallesen S, Bjorvatn B (2005): "Seasonal changes in mood and behaviour associated with gender, annual income and education: The Hordaland Health Study", European Journal of Epidemiology, Vol. 20(11): 929-37.

Oyane NM, Bjelland I, Pallesen S, Holsten F, Bjorvatn B (2008): "Seasonality is associated with anxiety and depression: The Hordaland Health Study", Journal of Affective Disorders, Vol. 105(1-3): 147-55.

Oyane NM, Ursin R, Pallesen S, Holsten F, Bjorvatn B (2008): "Self-reported seasonality is associated with complaints of sleep problems and deficient sleep duration: The Hordaland Health Study", Journal of Sleep Research, Vol. 17(1): 63-72.

Oyane NM, Ursin R, Pallesen S, Holsten F, Bjorvatn B (2010): "Increased health risk in subjects with high self-reported seasonality", PlosONE, 5(3): e9498.

Contents

1. Introduction

1.1 The concept of seasonality

Hippocrates once said ”Whoever wishes to investigate medicine properly, should proceed thus: in the first place to consider the seasons of the year, and what effects each of them produces for they are not at all alike, but differ much from themselves in regard to their changes” (“On air, Waters and Places”, approx 2500 years ago).

Hippocrates studied seasonal aspects of bipolar disease, and he observed mania to be most common in summer and melancholia to be most common in autumn. Later, the Greek Physician Aretaeus of Cappadocia (2nd century AD) described a beneficial effect of sunlight against lethargy in winter months. In the 19th and early 20th centuries, the concept of seasonality has occupated various researchers, and psychiatrists described a clinical syndrome characterized by recurrent depressions during winter.

The mood and behaviour of most individuals in the western countries vary by season to a certain degree (1-4), and this phenomenon is usually referred to as seasonality. Therefore, seasonality could be regarded as a normal phenomenon, and in many humans, seasonality is experienced only to a mild or negligible degree. However some individuals report extreme and sometimes disabling sensitivity to seasonal changes (2;3;5;6).

1.2 Seasonal Affective Disorder and its relationship to Seasonality

Around 1980, the researcher Herb Kern consulted his psychiatrist as he experienced recurring depressions during winter. Regular pharmacological treatment did not alleviate Kern's symptoms, but spring time did, as he never experienced depression during summer. Dr. Alfred Lewy at the American National Institute of Mental Health was contacted, as he had done research on biological rhythms and the effects of bright light treatment. He suggested three hours of bright light treatment before dusk and after dawn, which resulted in alleviation of Kern's symptoms after only three days of treatment. Dr. Lewy worked in a research group led by Dr. Norman Rosenthal, and they became aware that other patients also reported recurrent depressive episodes during winter. This could be a separate type of affective disorder, but at that time it seemed to be rather seldom among patients referred to psychiatrists. In 1981, Rosenthal and colleagues therefore published an article in the Washington Post describing the symptoms and invited subjects experiencing them to participate in a study. They received a nationwide response from thousands of people, and invited 29 subjects to participate. Based on this research, they described Seasonal Affective Disorder (SAD) (7). The subjects in the initial study experienced an atypical depression during winter, characterized by hypersomnia, hyperphagia and carbohydrate craving. Like in Kern's case, the symptoms were relieved as the subjects were exposed to artificial bright light (2500 lux) for three hours before dawn and three hours after dusk every day. Most of the subjects (93 %) in this study met diagnostic criteria for a bipolar disorder (mostly bipolar II) and experienced hypomanic or manic episodes during summer. Kasper and colleagues subsequently described a milder form of SAD also alleviated by bright light therapy, termed subsyndromal SAD (s-SAD) (3). During the last decades, numerous studies on SAD have been published, and the prevalence of manic/hypomanic episodes during summer has been less frequently reported.

The view of SAD as a separate disorder has been challenged by the dual vulnerability hypothesis (8;9). This hypothesis assumes seasonality to be a separate dimensional trait present in most humans. A high degree of seasonality, combined with a vulnerability to develop depression typically results in SAD (8). In contrast, sub-SAD is proposed to be a result of a higher susceptibility to seasonal changes, and to a lesser extent to depression (8).

In our research, we did not investigate SAD but rather measured seasonality as an independent trait in a sample of the general population. However, most previous studies in this field have investigated SAD specifically, and we here present some of the characteristics found in SAD subjects.

1.3 Sociodemographic characteristics of SAD patients

Similar to other affective disorders, SAD is more prevalent among women than men, with odds-ratios fluctuating between 1.5 and 4.0 (3;4;10). The age-group most commonly experiencing SAD appears to be early adult years (11;12), but results are diverging (10;12). As opposed to non-seasonal depression, SAD is reported to be more prevalent among subjects with a higher level of education and household income (10;13;14). Saarijärvi et al. (1999) conducted a study in northern Finland, where they compared seasonality between groups of subjects with different levels of education (10). They found higher overall seasonality in subjects with vocational education, college degree and university degree than in subjects with a lower education level. Eagles et al. (2002) reported a tendency of higher SAD-prevalence among more affluent subjects compared with other subjects (14). Subjects with a high annual income (equal to or above 70 000 dollars) in the US have a higher risk of suffering from SAD than other subjects (13). In contrast, some researchers have not reported any significant relationships between neither educational level nor annual income and SAD (4;15). Married subjects generally report less psychological distress than single or divorced subjects (16). Similar findings are also reported for SAD-subjects (17;18), however a study from Northern Finland did not show any significant relationships between marital status and prevalence of SAD (19).

1.4 Seasonality in mood disorders

In general, affective disorders have been reported to vary significantly between seasons in various studies based on self-report questionnaires and diagnostic interviews (15;20-23). When looking at depression, a peak prevalence of depressive symptoms has been reported during winter months in most epidemiological studies (15;22-24). On the other hand, in other studies (especially from Asian Communities) depression has been reported to be more common during summer than winter (25;26). Whether these discrepancies reflect differences in endogenous mood variability, climatic changes or cultural differences are unknown. A study among Asian women living in the UK reported higher depression scores during winter in Asian women born in Asia than in Asian women born in the UK, indicating some degree of acclimatization (23).

When it comes to anxiety disorders, general anxiety disorder, panic disorder, obsessive-compulsive disorder, tension-anxiety and substance abuse are reported to be most prevalent in autumn and winter months (20-22;27), while some authors do not find a peak of prevalence for anxiety disorders in any month (28;29).

SAD is not recognized as a separate disease in the DSM-IV, but it has been incorporated as one "pattern" of mood disturbances (30). This is in accordance with the dual vulnerability hypothesis, proposing seasonality to be a trait separate from depression. In the International Classification of Disease, tenth edition (ICD-10), Seasonal Affective Disorder is included in the diagnosis "Recurrent Depressive Disorder". Some comorbidity studies have found associations between SAD and other psychiatric disorders. Nevertheless, comorbidity between psychiatric disorders is an inevitable consequence of the structure of the DSM-IV, as it lacks most exclusionary rules that were included in the DSM-III-R (31). Anxiety disorders, including general anxiety disorder, social phobia and panic disorder are reported to be more common among SAD subjects than the general population and subjects with other mood disorders (32-34). Moreover, subjects with eating disorders have been reported to have a higher degree of seasonality and SAD than other subjects (3;35). Most of the subjects (93 %) in the initial study by Rosenthal and colleagues met diagnostic criteria for a bipolar disorder (mostly bipolar II) and experienced hypomanic or manic episodes during summer (36). However the prevalence of bipolar disorders has later been reported to be much lower among SAD-patients. A study from Norway found only 11% of SAD-patients to satisfy diagnostic criteria for bipolar disorder (37). When investigating axis II diagnoses in a sample of depressed SAD subjects, Reichborn-Kjennerud and colleagues reported that 58% of the sample satisfied diagnostic criteria for at least one personality disorder according to the DSM-IV, the most common being avoidant type (38). In the non-depressed state, 47% of the SAD subjects still satisfied diagnostic criteria for at least one personality disorder. Other studies have found a higher prevalence of neuroticism in subjects with SAD compared with other subjects (39-41). As earlier described, SAD subjects report other symptoms than commonly reported in regular depression, and some authors have suggested SAD subjects to have a unique personality profile (42;43).

1.5 Sleep disturbances associated with Seasonal Affective Disorder

Humans need sufficient sleep for optimal daily function. Sleep homeostasis denotes a basic principle of sleep function. Three decades ago, Borbely proposed a two-process model of sleep regulation, consisting of a homeostatic process (process S) and a circadian process (process C) (44). The homeostatic process reflects a physiological drive for sleep, and is increased with prolonged wakefulness, while the circadian process is endogenously generated by the suprachiasmatic nucleus in the hypothalamus and entrained by external cues such as daylight (45). Seasonal affective disorder and excessive seasonality might be linked to disturbances in one or both of these processes. Few studies have addressed these relationships directly, and results are diverging. In the original description of SAD by Rosenthal and colleagues, one of the atypical symptoms in his subjects was hypersomnia or increased sleep need. In a later cross-sectional study however, most SAD-subjects (80%) reported increased sleep during winter, but a minority (10%) reported decreased sleep (46). The same study reported sleep duration differences of more than two hours between summer and winter in SAD-patients (46). A study of SAD-patients in Canada found no correlation between hypersomnia and depression severity, and concluded that hypersomnia may not be a central feature of SAD (47).

Inconsistent resetting of the biological clock (Process C) is proposed to be an etiologic factor for SAD (48-50), as is impaired serotonin function, abnormal sensitivity to light and abnormal melatonin secretion (51-55). Some research has reported a delayed circadian rhythm in subjects with SAD, and this phase delay has been suggested to play a central role in the pathogenesis of the disease (56-58). However, this view is complicated by the fact that several studies have not shown a delayed phase shift in melatonin profile among SAD subjects (54;59;60).

Sleep homeostasis might also be disrupted in SAD-subjects. Cajochen and colleagues reported reduced build-up of sleepiness (Process S) in SAD-subjects compared with controls when kept awake for 40 hours and analyzing theta-alpha activity during wakefulness. This was probably due to increased sleepiness during the first 12 hours of wakefulness in SAD subjects (61). On the other hand, other studies have reported normal homeostatic sleep regulation among SAD patients (62;63).

When reviewing literature on the chronobiology in SAD, Levitan concluded that SAD is a result of several vulnerability factors acting at different levels, and not merely disturbances in sleep regulatory mechanisms (64).

1.6 Health risk factors in subjects with Seasonal Affective Disorder.

There are few studies investigating common health risk factors such as hypertension, obesity, smoking, low exercise level and high blood lipid level in subjects with SAD or high seasonality. Hyperphagia, increased carbohydrate craving and weight gain during winter are commonly reported symptoms among winter SAD-patients (7), and if the weight gain is not lost during summer, the consequence would be fat accumulation over the years. A health survey in the US reported that weight gain during winter in the general population is not completely lost during summer months (65). Since subjects with high seasonality tend to gain more weight during winter months, the risk for obesity is presumably increased compared with other subjects. A recent study by Rintamaki and colleagues reported waist circumference and prevalence of metabolic syndrome to increase with increasing seasonality (66).

Studies looking at associations between seasonality or SAD and blood lipid levels are scarce, and results are diverging. Post-hoc analyses in the study by Rintamaki and colleagues (66) did not reveal any significant associations between serum lipid levels and seasonality, while Pjrek and colleagues recently reported total cholesterol levels to be lower in SAD subjects than in non-seasonally depressed or schizophrenic patients (67). No associations are reported between seasonality or SAD and triglyceride levels. The theoretical significance of the link between blood lipid levels and mood disorders in general is unclear. Some authors have found cholesterol to be negatively associated with non-seasonal depression (68;69). Other authors report the opposite (70) or no relationship at all (71). In a study by Glueck and colleagues associations were found between depression and high triglyceride levels (72), although this finding was not replicated in another study including only men (73).

In summary, available literature suggests that SAD and high seasonality could be associated with a heightened risk of vascular disease. Smoking, little exercise and high alcohol consumption have also been reported to be associated with cardiovascular disease (74-77), and it is therefore interesting to investigate these health behaviours in subjects with high seasonality. As far as we know, this has not been done yet.

1.7 Aims of the study

1. To test the stability of the Global Seasonality Score, by investigating how it is affected by the season of questionnaire completion (Paper I).
2. To explore the general seasonality patterns and investigate relationships between seasonality and demographic factors (sex, education, annual income, marital status and urban/rural living) (Paper I).
3. To investigate if seasonality is positively correlated with non-seasonal depression and anxiety, and whether anxiety and depressive symptoms vary with the month of questionnaire completion (Paper II)

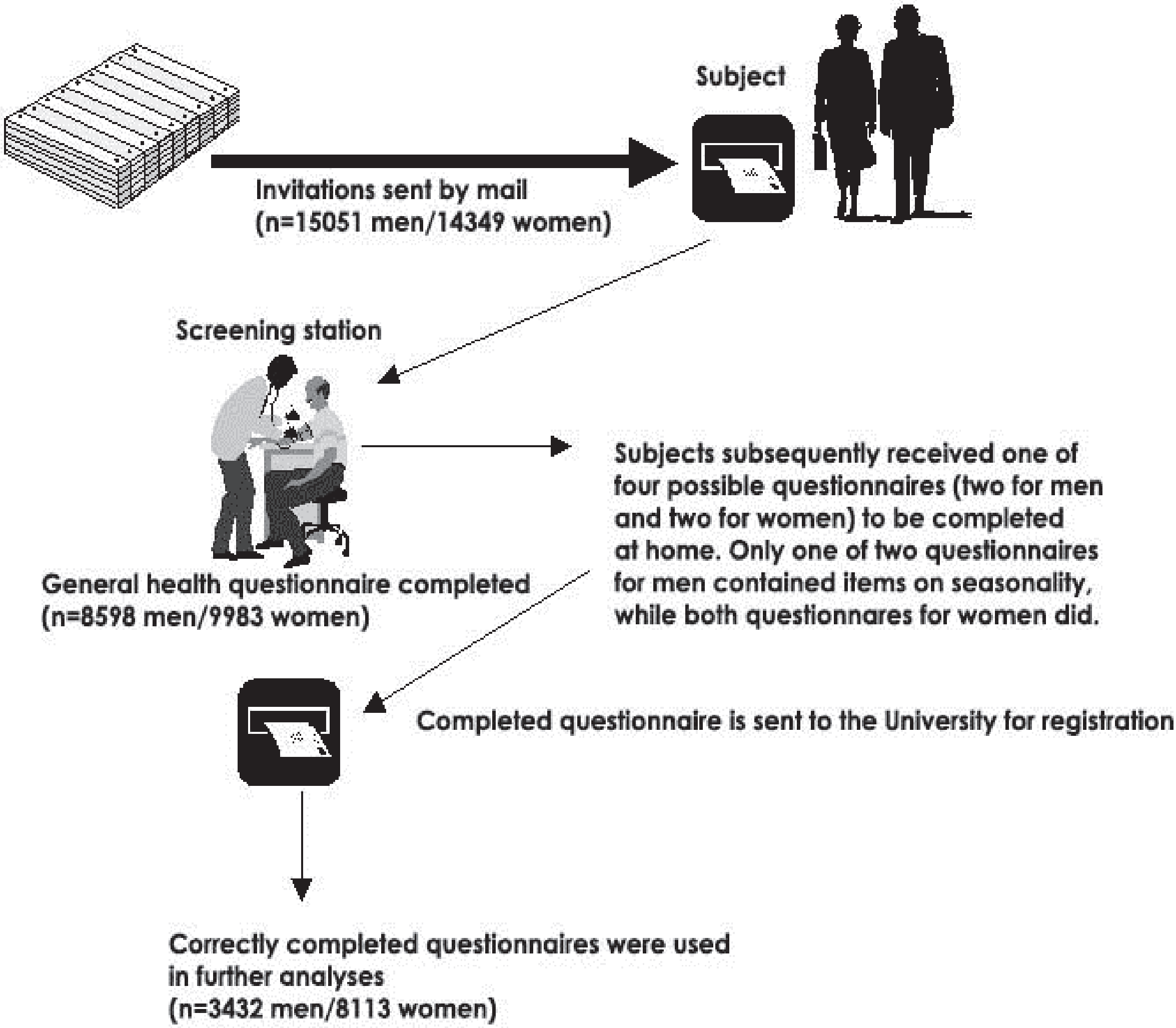
4. To investigate if sleep duration changes with different degrees of seasonality and whether subjects with high seasonality report more sleep difficulties compared with other subjects. We also wanted to explore whether any differences in sleep characteristics between subjects with high vs. low seasonality were specific to certain seasons or not (Paper III).
5. To look at associations between high seasonality, objective health measurements and health behaviours, and determine if high seasonality is associated with increased risk for cardiovascular disease (Paper IV).

2. Materials and methods

2.1 Procedure

The Hordaland Health Study '97-'99 (HUSK) was conducted during 1997-99 as a collaboration between the National Health Screening Service, the University of Bergen and local health services. The main objectives of this survey were to (1) identify potential health risk factors which may be modified to prevent disease, and (2) study epidemiologic tendencies of diseases in the population, in order to better prepare the country for future health-care needs.

Invitation letters were sent to all men (n=15051) and women (n=14349) aged 40-44 years in Hordaland county, situated 60 degrees north of equator. Totally 8598 men (57 % attendance rate) and 9983 women (70 % attendance rate) met at the screening station. Five questionnaires were used. A general health questionnaire was filled in by all participants at the screening station, which included questions concerning marital status, occupation, household income, education, an array of health complaints and various health behaviours. The subjects were subsequently randomized to receive one of four different questionnaires, two possible questionnaires for men and two possible questionnaires for women. For women, both questionnaires contained items on general degree of seasonal fluctuations in mood and behaviour (The Global Seasonality Score - GSS), whereas for men, GSS was included only in one of the two questionnaires due to logistic limitations. A sleep questionnaire was included in one of the questionnaires for men and one of the questionnaires for women. Questions concerning demographic factors (marital status, occupation, household income, education), anxiety and depression symptoms and various health behaviours were asked of all subjects. In sum, half of the men (randomly picked) and all women were offered the GSS questionnaire, half men and women were offered the sleep questionnaire, while all subjects were offered the other questionnaires analyzed in this study. The data collection lasted for one year, and the dates of questionnaire completion were noted by the staff receiving the questionnaire. Due to summer vacation among the staff, no subjects were interviewed in July, and few subjects were interviewed in August. The study protocol was approved by the Regional Ethics Committee and by the Norwegian Data Inspectorate.



2.2 Questionnaires

2.2.1 Global Seasonality Score (GSS) questionnaire

The Global Seasonality Score (GSS) was employed as a measure of seasonality among the respondents. It is the central feature of the Seasonal Pattern Assessment Questionnaire (SPAQ), introduced as a diagnostic or screening instrument for SAD by Casper et al (3). Due to space requirements, the complete SPAQ was not included in HUSK. The GSS has been shown to have an acceptable reliability and validity for screening seasonality in epidemiological studies (33;78-80). Additionally, the test-retest reliability is reported to be acceptable (2;3;81), being most reliable in extreme samples. We used an authorized Norwegian version of the questionnaire, translated by Dr. Lingjærde (University of Oslo). The cut-off levels of the GSS are usually set to 8-10 for sub-SAD and ≥11 for SAD as has been suggested by several studies (2;3;82-84). Based on the score, we defined the respondents in the current study as either having low (GSS < 8), moderate (GSS 8-10) or high (GSS ≥ 11) seasonality. A considerable concern has been that month of completion of the questionnaire seems to affect the GSS. The highest scores are reported when the questionnaire is completed during winter months (4;85).

To what degree do the following change ***with the seasons***?

		No change	**Slight Change**	**Moderate Change**	**Marked Change**	**Extremely Marked Change**
A. Sleep length						
B. Social activity						
C. Mood (overall feeling of well being)						
D. Weight						
E. Appetite						
F. Energy level						

2.2.2 Hospital Anxiety and Depression Scale (HADS)

HADS is a brief questionnaire, developed by Zigmond and Snaith to identify possible cases of anxiety and depression (86). The questionnaire contains seven items on anxiety (HADS-A) and seven items on depression (HADS-D), both referring to the last week. It has proven useful as a screening instrument for anxiety and depression in general populations (87). Each item is scored 0-3 depending on the severity of the actual symptom, giving a maximum score of 21 for each of the subscales. To estimate prevalence of possible anxiety and depression, we set the cut-off for both HADS-A and HADS-D ≥8. This value gives the optimal equilibrium between sensitivity and specificity, both found to be approximately 0.8 (87). Anxiety was defined as scores ≥8 on HADS-A, restricting the HADS-D to <8; depression was defined as scores ≥8 on HADS-D, restricting the HADS-A to <8. Subjects scoring ≥8 on both HADS-A and HADS-D were defined as having comorbid anxiety and depression.

2.2.3 Sleep questionnaire

Sleep was assessed using a modified version of the Karolinska Sleep Questionnaire, a widely used validated tool for investigating sleep characteristics (88-90). Variables included in this study were bedtime and rise time during the week and during free time, sleep latency in minutes during the week/free time and subjective sleep need (How much sleep do you need?) in hours and minutes. The following questions were answered on a 5-point scale (never, a few times per year, a few times per month, several times per week, always): problem falling asleep, problem with nightly awakenings, early morning awakening, fatigue/sleepiness, napping during the day, unintentional sleep episodes at work or during free time and fighting sleep.

We defined unintentional sleep episodes at work or during free time to be a problem if subjects answered the response alternatives “a few times per month”, “several times per week” or “always”. The remaining sleep complaints were defined to be a problem if subjects answered the response alternatives “several times per week” or “always”.

Mean sleep duration was defined as time in bed (calculated from bedtime and rise time) minus self-reported sleep latency (91). Sleep durations during the weekday and during free time were analyzed separately. As most subjects work five days per week, average sleep duration was calculated by multiplying weekday sleep duration with five, free time sleep duration with two and dividing the sum of both with seven. We defined sleep duration deficiency as subjective sleep need minus average sleep duration. A sleep duration deficiency of more than one hour is commonly considered pathological (92).

2.2.4 Objective health risk factors and health behaviours

Subjects’ height, weight, waist circumference and hip circumference were measured (shoes and outer garment were taken off) by study personnel. In addition, specially trained nurses measured blood pressure and collected blood samples. Systolic and diastolic blood pressures were measured in a relaxed sitting position following two minutes of rest. During the rest period the participants were told that three automated blood pressure measurements were to be performed, and that no talking was allowed during these measurements. The average of the last two measurements was used as the recorded blood pressure. Blood samples were collected non-fasting, and later analyzed for total-cholesterol, HDL-cholesterol, triglycerides and glucose.

All participants completed self-administered questionnaires with information on various health behaviours. Subjects were asked about the number of beers, glasses of wine and glasses of spirits consumed per two-week period, and the number of days per month they consumed alcohol. Questions concerning cigarette smoking (yes/no), and number of cigarettes smoked per day were also included. Subjects were asked about weekly quantities of low intensity exercise (not resulting in perspiration or short breath) and high intensity exercise (resulting in perspiration and short breath), with the following four possible answer categories; “0 hours”,” less than 1 hour”, “1-2 hours”, “3 hours or more”. Both exercise variables were dichotomized into exercising at least 3 hours per week vs. exercising less than 3 hours per week. Subjects were also asked whether or not they used medications for hypertension.

2.3 Statistics

2.3.1 Comparison between seasonality groups

When statistically testing differences between groups, parametric statistical tests generally require tested variables to be continuous with normally distributed values. In papers I-III, few parameters satisfied these criteria, and non-parametric testes were mostly used. We used the Kruskal-Wallis test for multiple comparisons, and Mann-Whitney U test to test for significant differences between groups. In paper I, mean GSS values were compared between different groups. Since we found the GSS to be skewed to the left with peaks for several values, non-parametric tests were used for all analyses. In paper II, values from the HADS were used, these were not continuous and non-parametric tests were also uniquely used.

In paper III, parametric testing (one-way ANOVA) was used for sleep duration parameters as they were normally distributed, while the Kruskal-Wallis test was used for the other variables (presence of sleep problems) as these were ordinal. In paper IV, a one-way ANOVA was used for the continuous data (BMI, waist-hip ratio, total cholesterol, HDL-cholesterol, triglycerides, glucose, systolic/diastolic blood pressure) while the Kruskal-Wallis was used for multiple comparisons for ordinal data (percentage of subjects exercising equal to or more than 3 hours per week and percentage of subjects being daily smokers). Post-hoc analyses were also performed using Least Significant Difference (LSD) correction.

2.3.2 Logistic regression analyses

In all papers binary logistic regression analyses were used to test associations between high seasonality (GSS≥11) and other variables. Odds-ratios were estimated directly from the regression coefficients, and the standard error of the regression coefficients were used to calculate the 95 % confidence intervals. In paper I, we explored how demographic factors predicted high seasonality (GSS≥11). Therefore, high seasonality was used as the dependent variable, while demographic factors (gender, annual income, education, marital status and urban/rural living) were used as independent variables. In all other papers, we wanted to look at how high seasonality predicted the different parameters. High seasonality was thus used as the independent variable and the other variables as dependent variables. Some continuous variables were either dichotomized or categorized to be used in the logistic regression models. In paper IV, logistic regression analyses were used for health behaviours only, while the objective health measurements were inserted as continuous variables in hierarchical logistic regression analyses (as described below).

2.3.3 Hierarchical multiple linear regression analyses

Hierarchical multiple linear regression analyses were performed to investigate associations between seasonality and objective health risk factors in paper IV. The objective health risk factors were used as dependent variables, and two blocks of independent variables were entered. The first block included the adjusting variables (month of questionnaire completion, marital status, income, education, living area and sleep duration), while the second block consisted of the Global Seasonality Score.

2.3.4 Effect of season of questionnaire completion

A central question in papers II-IV was whether the associations between seasonality, mood, sleep problems and health risk factors were confined to a certain time of year, or whether they persisted through all seasons. Several statistical analyses were performed to investigate this. In paper II, we used univariate general linear models for HADS-A and HADS-D separately using the HADS sum scores as dependent variable, while month of completion, seasonality (≥11 vs <11) and an interaction term including both were inserted as independent variables. For papers III and IV, month of filling in the questionnaire was regrouped into seasons; spring (March through May), summer (June through August), fall (September through November) and winter (December through February). A two-way ANOVA was run, using Season as one factor (having 4 levels) and GSS-group (having 3 levels) as the second factor. Sleep problems and sleep duration parameters comprised the dependent variables in paper III, while objective health measurements and health behaviours comprised the dependent variables in paper IV.

SPSS for Windows, version 12.0 was used for statistical analyses in paper I, version 13.0 was used in papers II and III and version 15.0 was used in paper IV. We stratified for gender in most statistical analyses and a two sided p-value <0.05 was chosen to indicate statistical significance.

3. Results

3.1.1 Paper I

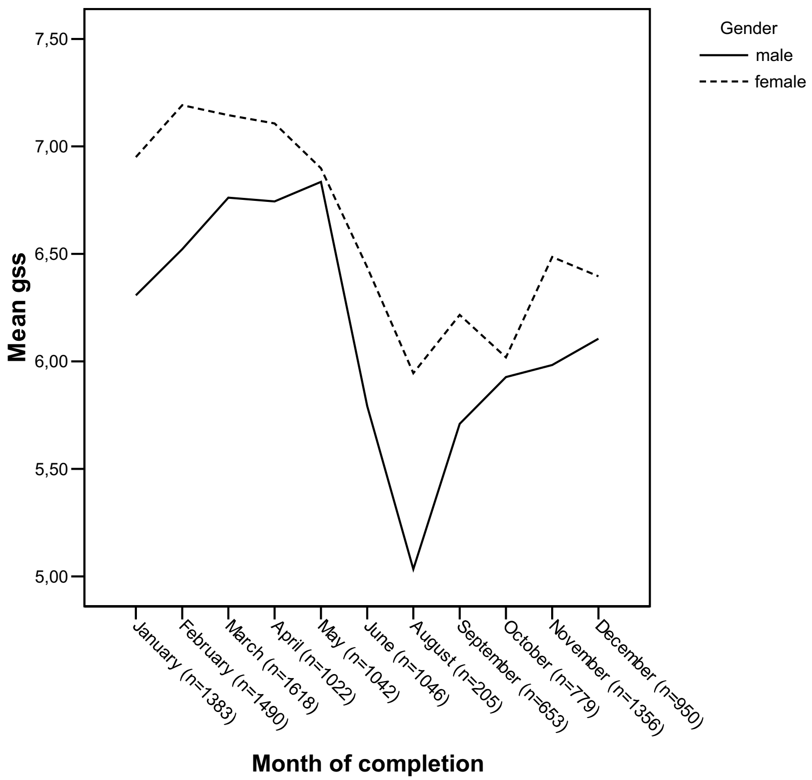
Associations between seasonality and demographic factors

High seasonality (GSS≥11) was reported by 18.4% of men and 22.2% of women, while moderate seasonality (GSS 8-10) was reported by 18.6% of men and 18.0% of women. Only 8.7% reported no seasonality (Scored 0 on the GSS). The frequency distributions of the Global Seasonality Scores were skewed to the left, and peaks were found for the values 6, 12, 18 and 24. Mean GSS was positively correlated with female gender, low annual income, low educational level and a marital status of single/divorced. In the adjusted logistic regression analyses, low annual income and a marital status of single/divorced were significant predictors of high seasonality (GSS≥11) in men, whereas low annual income and low educational level was significant predictors of high seasonality in women.

Seasonality related to month of assessment

The GSS varied significantly with which month the questionnaire was completed, and there were also significant changes when looking at the percentage of subjects reporting high seasonality (GSS≥11) in different months. Among women, 25.3% reported high seasonality in March, while 17.3% reported high seasonality in

October. Among men, the highest rate was reported in May and the lowest in August (24.8% and 8.3%, respectively).

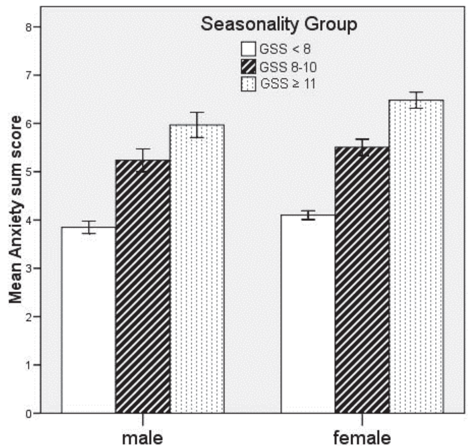


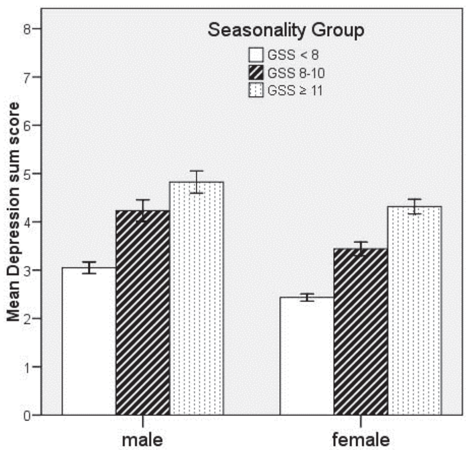
Variation of the Global Seasonality Score (GSS) as the questionnaire is completed in different months.

3.1.2 Paper II

Associations between seasonality and anxiety/depression

In the total sample, 12.6% of subjects were possible anxiety cases, 4.4% were possible depression cases, while 6.0% were possible cases of comorbid anxiety and depression. Increases in the GSS were associated with increases in both anxiety and depression sub-scores of the HADS. Furthermore, possible anxiety, depression and comorbid cases were more prevalent in the groups with a high (GSS≥11) or moderate (GSS=8-10) degree of seasonality than in the group with a low (GSS<8) degree of seasonality. Month of questionnaire completion did not affect the relationships between seasonality and anxiety/depression to a notable degree. The only statistical significant finding was modest variations in HADS-D mean sum scores in the group with a low or moderate degree of seasonality.



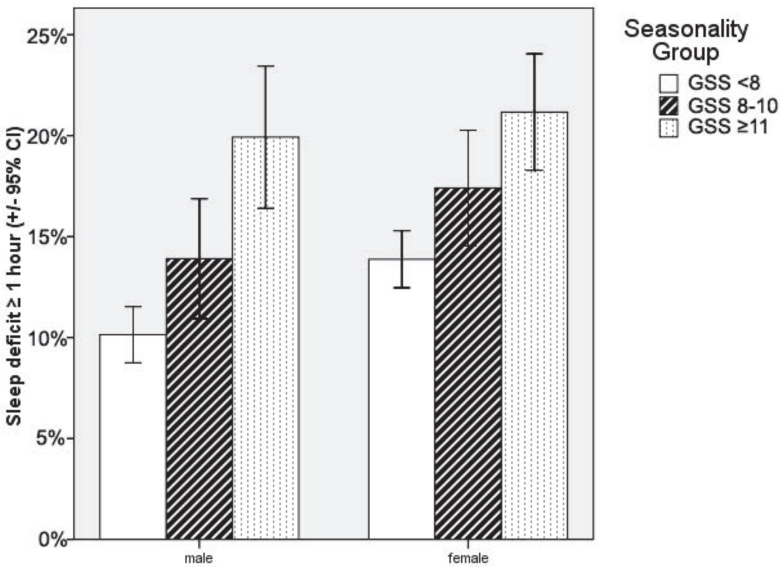


Mean sum scores of both the anxiety (HADS-A) and depression (HADS-D) subscales of the Hospital Anxiety and Depression Scale in different seasonality groups

3.1.3 Paper III

Sleep problems in different seasonality groups

Self-assessed sleep duration was slightly shorter among subjects with high seasonality than among subjects with moderate or low seasonality, while the opposite association was found between seasonality and subjective sleep need. Consequently, a long sleep duration deficiency (≥1 hour) was more prevalent in subjects with high seasonality (men: 20%, women: 21%) than in subjects with moderate (men: 14%, women: 17%) or low (men: 10%, women 14%) seasonality. The crude logistic regression analysis revealed a significant association between all sleep problems and high seasonality, while in the adjusted analysis early morning awakening was no longer significant for men. The analyses using the modified GSS (GSS not including the sleep item) resulted in similar results as the analyses using the total GSS scores.



The prevalence of a sleep deficiency (subjective sleep need – average sleep duration) of more than one hour in different seasonality groups. GSS= Global Seasonality Score, CI=Confidence Interval.

Effect of season of interview

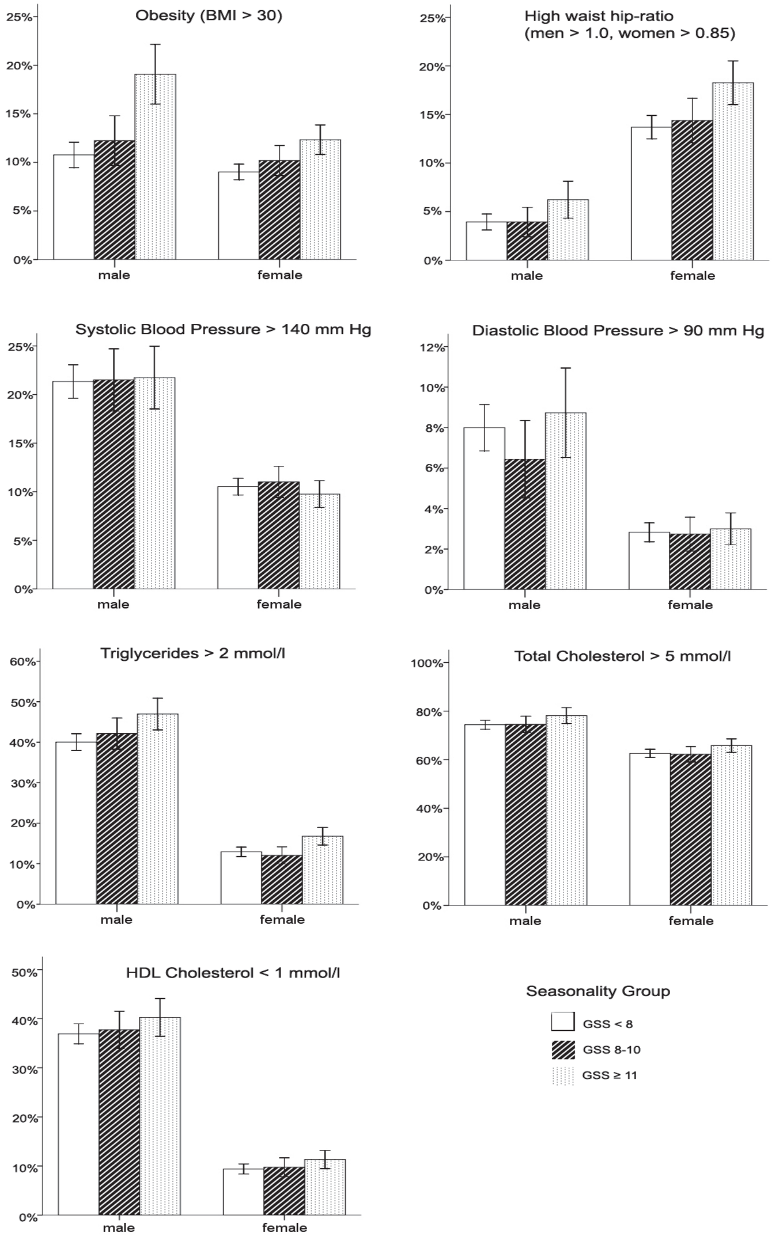
Overall, there were relatively small effects of season of interview on sleep parameters, and the clinical significance was uncertain. The interaction term (Season x GSS-group) was significant for problem falling asleep and early morning awakening in men, while it was significant for problem falling asleep and insufficient sleep in women.

3.1.4 Paper IV

Objective health measurements and health behaviours in the different GSS groups

In both men and women, increasing GSS was positively associated with various objective health risk factors and health behaviours associated with cardiovascular disease.

In the hierarchical multiple linear regression analysis, increasing GSS was significantly associated with increasing waist-hip ratio, BMI, triglycerides and decreasing HDL-cholesterol in both men and women. In men, increasing GSS was also significantly associated with increasing total cholesterol. The interaction term seasonality group*season was significantly associated with systolic blood pressure in both gender and BMI in women. Systolic blood pressure was lower during summer in subjects reporting high seasonality compared with subjects reporting low seasonality. In women, BMI varied more across seasons in subjects with high seasonality than in subjects with low seasonality, but remained higher in the high seasonality group than the low seasonality group in all seasons. Seasonality was significantly and negatively associated with low and high intensity exercise and positively associated with daily cigarette smoking in women. In men, no significant associations were found between high seasonality and health behaviours and the interaction term seasonality group*season was not significantly associated with any of the health behaviours.



Objective health measures associated with risk of cardiovascular disease in different seasonality groups. Each chart has prevalence of health risks on the vertical axis and seasonality group on the horizontal axis, and results for men and women are shown separately. GSS=Global Seasonality Score. Vertical lines depict the 95 % Confidence interval.

4. Discussion

4.1 Summary of findings

We found high seasonality to be common in our population, as it was reported by 18.4 % of men and 22.2 % of women. Low annual income and a marital status of single/divorced were significant predictors of high seasonality in men, whereas low annual income and low educational level were significant predictors of high seasonality in women. Increases in seasonality were associated with increases in symptom scores for both anxiety and depression, irrespective of month of questionnaire completion. Additionally, high seasonality was associated with a higher prevalence of various sleep complaints, and subjects with high seasonality slept less than subjects with moderate or low seasonality. The sleep duration did not vary to a notable degree between the different months in any of the different seasonality groups. Subjects with high seasonality had more objective health risk factors associated with cardiovascular disease, as increasing GSS was significantly associated with increasing waist-hip ratio, BMI, triglycerides, total cholesterol and decreasing HDL-cholesterol. Additionally, high seasonality was significantly associated with cigarette smoking and less exercise in women.

4.2 Methodological considerations

To our knowledge, this is the largest study on seasonality to date. It is an advantage that this study is a part of a larger health survey of a normal population, since it minimizes selection bias and increases external validity. Many studies of SAD use patient populations, which tend to over-estimate the prevalence of comorbidity as subjects with more than one disorder more frequently seek treatment (93). Consequently, selection bias has been a major problem in most epidemiologic research in this area. On the other hand, the generalization of our results is limited since only subjects aged 40-44 years were invited to participate. This may influence our results and further studies including all age groups should be done before generalizing conclusions. Statistical power differences between genders can also have affected our results. The greater number of significant findings in women than men could be caused by the differences in sample sizes.

A cross-sectional design as used in this study also results in limitations, especially the fact that it is impossible to test causal relationships. Additionally, the GSS questionnaire is subject to recall bias. This is demonstrated by the fact that results were affected by the month of completion of the questionnaire; subjects tend to under-estimate seasonal vulnerability when asked in summer months (4;85;94). Depressive mood at the time of filling in the questionnaire could also influence how subjects report seasonal effects (95).

The number of non-attendants could also affect our results, as 43% of invited men and 30% of invited women did not attend the screening station. In a health survey in northern Norway, psychiatric disorders were more than twice as common among non-attendants than attendants (96), while differences in the prevalence between men and women and between marital statuses were shown to be quite robust despite the effect of non-attendance. Consequently, we may assume that prevalence estimates of seasonality and SAD are generally underestimated in population studies, whereas the effects of sex, marital status and other demographic factors are more reliable.

As all the data in the present study were based upon self report, any significant association may to a certain degree reflect a underlying disposition of negative affectivity, leading to a potential overestimation of the true association between different self-reported outcomes (97). We did not ask the subjects whether they regarded seasonality to be a problem. Nevertheless, this is not a major concern since we primarily intended to investigate the phenomenon of seasonality rather than SAD. Subjects were not asked which months they experienced most changes in mood and behaviour, and high seasonality could reflect a clinical picture resembling both winter and summer depression. Nonetheless, considering the effect of month of completion discussed earlier, we can assume that most of the participants reporting seasonal changes experience most symptoms during winter months. In addition, summer-SAD has been shown to be far less prevalent than winter-SAD in northern latitudes (98).

Due to practical reasons, the blood samples presented in paper IV were taken non-fasting. Since glucose, triglyceride and total cholesterol concentrations can be affected by recent food intake, this weakens the accuracy and precision of these measurements. Consequently, confidence intervals broaden and the chance of finding significant associations with seasonality decreases.

4.3 Effect of season on the Global Seasonality Score

Seasonality is a general pattern and not supposed to be confined to any certain period of the year, and the score on GSS should therefore not differ due to month of completion as reported in paper I. Our findings are consistent with another study in Norway by Lund and Hanssen (2001), reporting significant differences in SAD prevalence depending on which month the SPAQ questionnaire was completed. The estimated SAD prevalence peaked in March (14.4 %) and was lowest in September (5.6 %) (85). Mersch and colleagues (1999) sent SPAQ to 200 subjects every month through the year, and found GSS to be lower when the questionnaire was completed in summer compared with winter months (4). Most of our participants (57%) answered the GSS questionnaire in late winter and spring, and the overall seasonality might have been slightly overestimated. The effect of month of completion on the GSS should be considered when evaluating other studies using SPAQ. More recently, a new questionnaire measuring seasonality, the Seasonal Health Questionnaire has been introduced, and it has been reported to have higher specificity and sensitivity than the SPAQ for the detection of SAD in a general practice (99;100). Hence, this new questionnaire could prove to be useful in future epidemiologic research on seasonality.

4.4 Clinical significance of our results

In a population-based study as the present one, it is important to distinguish between clinical and statistical significance of our findings. Since seasonality is common in the general population, even small effect sizes might represent considerable public health consequences including health economical concerns. From an epidemiological point of view, results from cross-sectional surveys are best suited to generate hypotheses. Longitudinal studies on the other hand, are more suitable to test such hypotheses. Nevertheless, we here try to explain our results from a clinical point of view. We found high seasonality to be more prevalent in women than men; however the difference was much smaller than the reported differences in SAD-prevalence between men and women (3;4;10). This could indicate that women tend to find relatively similar seasonal variations more problematic than men. As described in the introduction section, SAD has been reported to have demographic characteristics quite different from traditional mood disorders, as SAD tends to be more prevalent among subjects with higher education, annual income and sociodemographic status. In contrary to this, we found high seasonality per se to be most prevalent among subjects with low annual income and low education. The reason for this discrepancy is uncertain. A possible explanation is that working subjects find high seasonality to be a greater burden than unemployed subjects, thus fulfilling criteria for SAD more often despite lower seasonality scores. Conversely, it is also possible that people experiencing high seasonality have less chance of choosing a long education or apply for a demanding job.

It would be expected that subjects with high seasonality would report different prevalences of affective disorders in different seasons, however this was not the case among our subjects, since there was an association between high seasonality and depression regardless of season of questionnaire completion It should be noted that the HADS questionnaire used in our study measures symptom load without resulting in any exact depression or anxiety diagnoses. Our results resemble those from a study by Mersch et al (1999) in the Netherlands using a different depression questionnaire (4). Furthermore, Parslow et al (2004) found no difference in Goldberg Depression Score between summer and winter in subjects with high seasonality (GSS≥11) (95). In addition, we found an association between seasonality and anxiety, as previously reported in other epidemiological studies (33;101). We cannot tell cause from effect, but seasonality could be a separate dimensional trait associated with anxiety and depression. On the other hand, mood in subjects with anxiety and depression could be more affected by seasonal changes in general. The effects of negative affectivity discussed earlier could also play an important role.

Originally, the SAD symptom complex was thought to include hypersomnia (7;56;102), but according to our results subjects with high seasonality reported more insomnia symptoms than subjects with moderate/low seasonality. We reported significantly higher sleep duration deficiency and complaints of sleep problems in subjects with high seasonality compared with other subjects, regardless of month of questionnaire completion. Nevertheless, our results also indicate that some subjects with high seasonality might experience hypersomnia, as unintentional daytime sleep episodes were more frequent in subjects with high seasonality compared with other subjects. Additionally, long sleep duration (as well as short sleep duration) was associated with high seasonality in women. An important question in this context is whether subjects reporting hypersomnia actually sleep more or if they merely feel more sleepy. SAD-patients have actually been reported to show less slow wave sleep in winter compared with summer (46), and a study using actigraphy found lower sleep efficiency in SAD-subjects compared with controls (50). A central issue is whether confounding factors associated with high seasonality also could lead to sleep problems. For instance, the severity of some chronic diseases such as rheumatoid arthritis and obstructive lung disease show seasonal variations, as well as various psychiatric disorders.

The health risk factors (high BMI, high waist-hip ratio, high triglyceride level and low HDL-cholesterol level) associated with seasonality in our study are also associated with vascular disease and the metabolic syndrome (103). However, we did not find any relationships between seasonality and hypertension, which is usually present in subjects with the metabolic syndrome. Unhealthy behaviour (little exercise and cigarette smoking) was also more prevalent in women with high seasonality than other women, resulting in an even higher risk for cardiovascular disease.

Several hypotheses could explain these associations. Seasonality could lead to increasing psychological distress, which is reported to be associated with health risk factors (104). SAD has been proposed to possibly suppress the immune system and affect the risk of having cardiovascular disease during winter (105). Additionally, low levels of outdoor light exposure during winter months might cause inadequate resetting of the circadian clock, which presumably is linked to obesity (106). Finally, several chronic diseases worsen in winter (as discussed in the previous paragraph), and this could increase immobility and obesity (107;108).

4.5 Ethical aspects of defining seasonality as a trait

During the last decades, public health researchers have expressed concern about the increased medicalization in the society. Medicalization has been described as "a process by which nonmedical problems become defined and treated as medical problems, usually in terms of illness and disorders" (109). About a fifth of subjects in the Hordaland Health Study reported changes in mood and behaviour to a high degree, and another fifth reported these changes to a moderate degree. However, seasonality per se should not be considered as a disease or as a "unhealthy" phenomenon, in contrast to seasonal affective disorder. Even subjects with a high or extreme degree of seasonality might cope well with it, and should not be characterized as being ill or diseased. Consequently, high seasonality per se does not necessarily require any form of treatment.

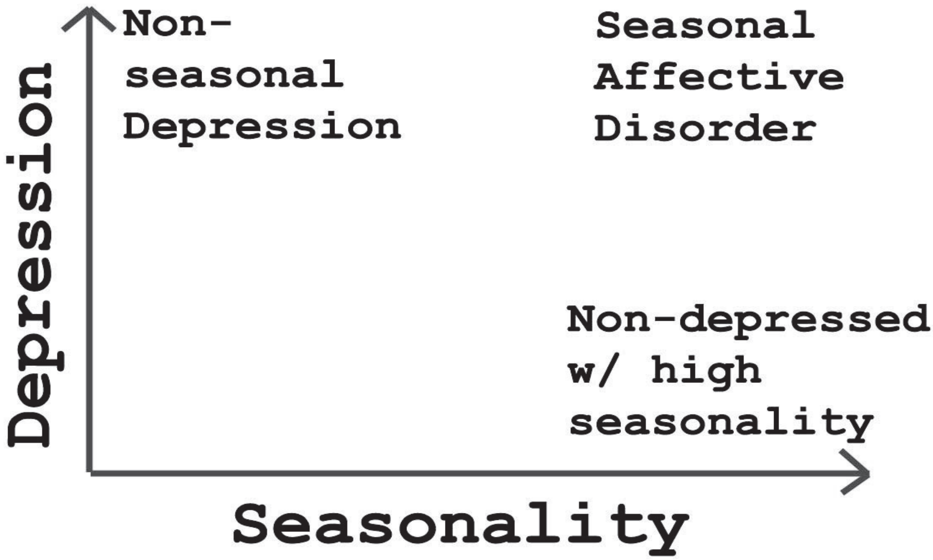
4.6 Concluding remarks and suggestions for future research

Due to our cross-sectional design, no conclusions concerning causal relationships can be drawn, but I would like to present some hypotheses in order to explain our results. As already mentioned, seasonality is not the same as SAD. Seasonality can be looked at as a normal phenomenon present in most humans to a certain degree, while SAD is a syndrome requiring subjects to have repeated major depressive episodes during a certain time of year. In our analyses we handled seasonality as a separate trait by grouping subjects according to their Global Seasonality Score. This is in accordance with the principles of the dual vulnerability hypothesis for SAD, where the syndrome is thought to be the result of vulnerability to both depression and seasonality (8).

Interestingly, our results show that subjects with high seasonality did not share the same characteristics as previously reported in SAD subjects. In paper I, we found high seasonality to be associated with low income and low education, while SAD tends to be most common in subjects with high socioeconomic status. In paper II, we found subjects with high seasonality to score higher on anxiety and depression symptoms than other subjects throughout the year, not only during certain seasons. In paper III, sleep duration was a little shorter in subjects with high seasonality compared to other subjects, in contrast to the fact that hypersomnia has traditionally been described in SAD subjects. These discrepancies support the view of seasonality being a separate dimensional trait and not merely a part of SAD.

It is logical to expect that high or extreme seasonality could be distressing to subjects even if they are not simultaneously depressed. In paper IV, we discussed possible beneficiary effects of seasonality for our ancestors, which could be the reason why most humans experience seasonality to a certain degree. However, in the modern society a high degree of seasonality is probably a disadvantage (110). Subsyndromal SAD is already described as a syndrome with a moderate or high degree of seasonality without a major depressive episode (3). Bright light therapy has proved to be effective also for this group, effect sizes being as good as or better than those reported for SAD-patients (111). Studies investigating bright light therapy against non-seasonal depression have shown conflicting results, but in a meta-analysis bright light had a significant overall effect, although lower than for SAD (112). Some subjects with depressive symptoms could possibly have an additional seasonal component, which in turn could be alleviated by bright light treatment. We reported in paper II that high seasonality is a possible risk factor for depression irrespective of season, and this could explain why depressive symptoms alleviate as the seasonal component is treated. In this context, a subgroup of winter SAD-subjects with residual depression during the summer has been described, and the effect of bright light treatment has been reported, although less than for typical SAD subjects (8). The authors of that paper suggest that the group with incomplete summer remission

has a high vulnerability for depression and a smaller susceptibility for seasonal changes.
The dual vulnerability hypothesis can be illustrated as a chart with depression vulnerability on the y-axis and seasonality on the x-axis.



Subjects with traditional seasonal affective disorder would be placed somewhere on the upper right hand corner, those with non-seasonal depression would be placed somewhere in the upper left hand corner, while non-depressed subjects with high seasonality would be placed somewhere in the lower right hand corner. Their exact location would be determined by the degree of seasonality and depression vulnerability. Future population-based studies using tools to grade seasonality and mood disorders separately in a population are necessary to confirm this model. Furthermore, a prospective design is needed in order to explore the causal relationships between high seasonality, depression, anxiety, sleep problems and health behaviours. Indeed, high seasonality is so common that a prospective cohort study should be feasible.

Source of data

(1) Dam H, Jakobsen K, Mellerup E. Prevalence of winter depression in Denmark. *Acta Psychiatrica Scandinavica* 1998; 97(1):1-4.

(2) Hardin TA, Wehr TA, Brewerton T, Kasper S, Berrettini W, Rabkin J et al. Evaluation of seasonality in six clinical populations and two normal populations. *Journal of Psychiatric Research* 1991; 25(3):75-87.

(3) Kasper S, Wehr TA, Bartko JJ, Gaist PA, Rosenthal NE. Epidemiological findings of seasonal changes in mood and behavior. A telephone survey of Montgomery County, Maryland. *Archives of General Psychiatry* 1989; 46(9):823-833.

(4) Mersch PP, Middendorp HM, Bouhuys AL, Beersma DG, Van Den Hoofdakker RH. The prevalence of Seasonal Affective Disorder in The Netherlands: a Prospective and Retrospective Study of Seasonal Mood Variation in the General Population. *Biological Psychiatry* 1999; 45:1013-1022.

(5) Elbi H, Noyan A, Korukoglu S, Unal S, Bekaroglu M, Oguzhanoglu N et al. Seasonal Affective Disorder in Eight Groups in Turkey: a Cross-National perspective. *J Affect Disord* 2002; 70:77-84.

(6) Michalak EE, Tam EM, Manjunath CV, Lewy AJ, Levitran RD, Lam RW. Quality of life in patients with seasonal affective disorder: summer vs winter scores. *Can J Psychiatry* 2005; 50(5):292-295.

(7) Rosenthal NE, Sack DA, Gillin JC, Lewy AJ, Goodwin FK, Davenport Y et al. Seasonal Affective Disorder: A Description of the Syndrome and Preliminary Findings With Light Therapy. *Archives of General Psychiatry* 1984; 41:72-80.

(8) Lam RW, Tam EM, Yatham LN, Shiah IS, Zis AP. Seasonal depression: The dual vulnerability hypothesis revisited. *Journal of Affective Disorders* 2001; 63:123-132.

(9) Young MA, Watel LG, Lahmeyer HW, Eastman CI. The temporal onset of individual symptoms in winter depression: differentiating underlying mechanisms. *Journal of Affective Disorders* 1991; 22(4):191-197.

(10) Saarijarvi S, Lauerma H, Helenius H, Saarilehto S. Seasonal affective disorders among rural Finns and Lapps. *Acta Psychiatr Scand* 1999; 99(2):95-101.

(11) Eagles JM, Andrew JE, Wileman SM, Howie FL, Cameron IM, Naji SA. Seasonal affective disorder and social deprivation in Aberdeen. *J Affect Disord* 2002; 70(3):337-340.

(12) Mersch PP, Middendorp HM, Bouhuys AL, Beersma DG, van den Hoofdakker RH. The prevalence of seasonal affective disorder in The Netherlands: a prospective and retrospective study of seasonal mood variation in the general population. *Biol Psychiatry* 1999; 45(8):1013-1022.

(13) Blazer DG, Kessler RC, Swartz MS. Epidemiology of recurrent major and minor depression with a seasonal pattern. The National Comorbidity Survey. *Br J Psychiatry* 1998; 172:164-167.

(14) Eagles JM, Wileman SM, Cameron IM, Howie FL, Lawton K, Gray DA et al. Seasonal affective disorder among primary care attenders and a community sample in Aberdeen. *Br J Psychiatry* 1999; 175:472-475.

(15) Palinkas LA, Cravalho M, Browner D. Seasonal variation of depressive symptoms in Antarctica. *Acta Psychiatrica Scandinavica* 1995; 91(6):423-429.

(16) Hope S, Rodgers B, Power C. Marital status transitions and psychological distress: longitudinal evidence from a national population sample. *Psychol Med* 1999; 29(2):381-389.

(17) Eagles JM, Andrew JE, Wileman SM, Howie FL, Cameron IM, Naji SA. Seasonal affective disorder and social deprivation in Aberdeen. *J Affect Disord* 2002; 70(3):337-340.

(18) Mersch PP, Middendorp HM, Bouhuys AL, Beersma DG, van den Hoofdakker RH. The prevalence of seasonal affective disorder in The Netherlands: a prospective and retrospective study of seasonal mood variation in the general population. *Biol Psychiatry* 1999; 45(8):1013-1022.

(19) Saarijarvi S, Lauerma H, Helenius H, Saarilehto S. Seasonal affective disorders among rural Finns and Lapps. *Acta Psychiatr Scand* 1999; 99(2):95-101.

(20) de Graaf R, van Dorsselaer S, ten Have M, Schoemaker C, Vollebergh WA. Seasonal variations in mental disorders in the general population of a country with a maritime climate: findings from the Netherlands mental health survey and incidence study. *American Journal of Epidemiology* 2005; 162(7):654-661.

(21) Harmatz MG, Well AD, Overtree CE, Kawamura KY, Rosal M, Ockene IS. Seasonal variation of depression and other moods: a longitudinal approach. *Journal of Biological Rhythms* 2000; 15(4):344-350.

(22) Schlager D, Schwartz JE, Bromet EJ. Seasonal variations of current symptoms in a healthy population. *British Journal of Psychiatry* 1993; 163:322-326.

(23) Suhail K, Cochrane R. Seasonal changes in affective state in samples of Asian and white women. *Social Psychiatry and Psychiatric Epidemiology* 1997; 32(3):149-157.

(24) Haggag A, Eklund B, Linaker O, Gotestam KG. Seasonal mood variation: an epidemiological study in northern Norway. *Acta Psychiatrica Scandinavica* 1990; 81(2):141-145.

(25) Han L, Wang K, Du Z, Cheng Y, Simons JS, Rosenthal NE. Seasonal variations in mood and behavior among Chinese medical students. *Am J Psychiatry* 2000; 157(1):133-135.

(26) Ozaki N, Ono Y, Ito A, Rosenthal NE. Prevalence of seasonal difficulties in mood and behavior among Japanese civil servants. *Am J Psychiatry* 1995; 152(8):1225-1227.

(27) Kovalenko PA, Hoven CW, Wicks J, Moore RE, Mandell DJ, Liu H. Seasonal variations in internalizing, externalizing, and substance use disorders in youth. *Psychiatry Research* 2000; 94(2):103-119.

(28) Magnusson A, Axelsson J, Karlsson MM, Oskarsson H. Lack of seasonal mood change in the Icelandic population: results of a cross-sectional study. *American Journal of Psychiatry* 2000; 157(2):234-238.

(29) Posternak MA, Zimmerman M. Lack of association between seasonality and psychopathology in psychiatric outpatients. *Psychiatry Res* 2002; 112(3):187-194.

(30) American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV, 4th edn. 1994. Washington, DC, American Psychiatric Press.
Ref Type: Serial (Book,Monograph)

(31) Boyd JH, Burke JD, Jr., Gruenberg E, Holzer CE, III, Rae DS, George LK et al. Exclusion criteria of DSM-III. A study of co-occurrence of hierarchy-free syndromes. *Arch Gen Psychiatry* 1984; 41(10):983-989.

(32) Levitt AJ, Joffe RT, Brecher D, MacDonald C. Anxiety disorders and anxiety symptoms in a clinic sample of seasonal and non-seasonal depressives. *J Affect Disord* 1993; 28(1):51-56.

(33) Magnusson A. Validation of the Seasonal Pattern Assessment Questionnaire (SPAQ). *Journal of Affective Disorders* 1996; 40(3):121-129.

(34) Thompson C, Isaacs G. Seasonal affective disorder--a British sample. Symptomatology in relation to mode of referral and diagnostic subtype. *J Affect Disord* 1988; 14(1):1-11.

(35) Brewerton TD, Krahn DD, Hardin TA, Wehr TA, Rosenthal NE. Findings from the Seasonal Pattern Assessment Questionnaire in patients with eating disorders and control subjects: effects of diagnosis and location. *Psychiatry Res* 1994; 52(1):71-84.

(36) Rosenthal NE, Sack DA, Gillin JC, Lewy AJ, Goodwin FK, Davenport Y et al. Seasonal affective disorder. A description of the syndrome and preliminary findings with light therapy. *Arch Gen Psychiatry* 1984; 41(1):72-80.

(37) Lingjaerde O, Reichborn-Kjennerud T. Characteristics of winter depression in the Oslo area (60 degrees N). *Acta Psychiatr Scand* 1993; 88(2):111-20.

(38) Reichborn-Kjennerud T, Lingjaerde O, Dahl AA. Personality disorders in patients with winter depression. *Acta Psychiatr Scand* 1994; 90(6):413-419.

(39) Bagby RM, Schuller DR, Levitt AJ, Joffe RT, Harkness KL. Seasonal and non-seasonal depression and the five-factor model of personality. *J Affect Disord* 1996; 38(2-3):89-95.

(40) Jain U, Blais MA, Otto MW, Hirshfeld DR, Sachs GS. Five-factor personality traits in patients with seasonal depression: treatment effects and comparisons with bipolar patients. *J Affect Disord* 1999; 55(1):51-54.

(41) Jang KL, Lam RW, Livesley WJ, Vernon PA. The relationship between seasonal mood change and personality: more apparent than real? *Acta Psychiatr Scand* 1997; 95(6):539-543.

(42) Pendse B, Westrin A, Engstrom G. Temperament traits in seasonal affective disorder, suicide attempters with non-seasonal major depression and healthy controls. *J Affect Disord* 1999; 54(1-2):55-65.

(43) Schuller DR, Bagby RM, Levitt AJ, Joffe RT. A comparison of personality characteristics of seasonal and nonseasonal major depression. *Compr Psychiatry* 1993; 34(5):360-362.

(44) Borbely AA. A two process model of sleep regulation. *Hum Neurobiol* 1982; 1(3):195-204.

(45) Edmunds LN Jr. Cellular and Molecular Bases of Biological Clocks: Models and Mechanisms for Circadian Timekeeping. New York: Springer-Verlag, 1988.

(46) Anderson JL, Rosen LN, Mendelson WB, Jacobsen FM, Skwerer RG, Joseph-Vanderpool JR et al. Sleep in fall/winter seasonal affective disorder: effekcts of light and changing seasons. *J Psychosom Res* 1994; 38(4):323-337.

(47) Shapiro CM, Devins GM, Feldman B, Levitt AJ. Is hypersomnolence a feature of seasonal affective disorder? *J Psychosom Res* 1994; 38(Suppl1):49-54.

(48) Partonen T, Lönnqvist J. Seasonal affective disorder. *Lancet* 1998; 352:1369-1374.

(49) Teicher MH, Glod CA, Magnus E. Circadian rest-activity distrubances in seasonal affective disorder. *Arch Gen Psychiatry* 1997; 54:124-130.

(50) Winkler D, Pjrek E, Praschak-Rieder N, Willeit M, Pezawas L, Konstantinidis A et al. Actigraphy in patients with seasonal affective disorder and healthy control subjects treated with light therapy. *Biol Psychiatry* 2006; 58(4):331-336.

(51) Oren DA, Moul DE, Schwartz PJ, Alexander JR, Yamada EM, Rosenthal NE. An investigation of ophtalmic function in winter seasonal affective disorder. *Depression* 1993; 1:29-37.

(52) Thompson C, Stinson D, Smith A. Seasonal affective disorder and season-dependent abnormalities of melatonin suppression by light. *Lancet* 1990; 336(8717):703-706.

(53) Neumeister A, Turner EH, Matthews JR. Effects of tryptophan depletion vs catecholamine depletion in patients with seasonal affective disorder in remission with light therapy. *Arch Gen Psychiatry* 1998; 55:524-530.

(54) Káradóttir R, Axelsson J. Melatonin secretion in SAD patients and healthy subjects matched with respect to age and sex. *Int J Circumpolar Health* 2001; 60:548-551.

(55) Lewy AJ, Lefler BJ, Emens JS, Bauer VK. The circadian basis of winter depression. *Proc Natl Acad Sci USA* 2006; 103(19):7414-7419.

(56) Magnusson A, Boivin D. Seasonal affective disorder: an overview. *Chronobiol Int* 2003; 20(2):189-207.

(57) Lewy AJ, Sack RL, Singer CM, White DM, Hoban TM. Winter depression and the phase-shift hypothesis for bright light's therapeutic effects: history, theory, and experimental evidence. *J Biol Rhythms* 1988; 3(2):121-134.

(58) Avery DH, Dahl K, Savage MV, Brengelmann GL, Larsen LH, Kenny MA et al. Circadian temperature and cortisol rhythms during a constant routine

are phase-delayed in hypersomnic winter depression. *Biol Psychiatry* 1997; 41(11):1109-1123.

(59) Thompson C, Childs PA, Martin NJ, Rodin I, Smythe PJ. Effects of morning phototherapy on circadian markers in seasonal affective disorder. *Br J Psychiatry* 1997; 170:431-435.

(60) Koorengevel KM, Beersma DG, Den Boer JA, Van Den Hoofdakker RH. A forced desynchrony study of circadian pacemaker characteristics in seasonal affective disorder. *J Biol Rhythms* 2002; 17(5):463-475.

(61) Cajochen C, Brunner DP, Kräuchi K, Graw P, Wirz-Justice A. EEG and Subjective Sleepiness during Extended Wakefulness in Seasonal Affective Disorder: Circadian and Homeostatic Influences. *Biol Psychiatry* 2000; 47:610-617.

(62) Brunner DP, Kräuchi K, Dijk DJ, Leonhardt G, Haug HJ, Wirz-Justice A. Sleep EEG in seasonal affective disorder and control women: Effects of midday light treatment and sleep deprivation. *Biol Psychiatry* 1996; 40:485-496.

(63) Koorengevel KM, Beersma DG, Den Boer JA, Van Den Hoofdakker RH. Sleep in seasonal affective disorder patioents in forced desynchrony: an explorative study. *J Sleep Res* 2002; 11(4):347-356.

(64) Levitan RD. The chronobiology and neurobiology of winter seasonal affective disorder. *Dialogues Clin Neurosci* 2007; 9(3):315-324.

(65) Yanovski JA, Yanovski SZ, Sovik KN, Nguyen TT, O'Neil PM, Sebring NG. A prospective study of holiday weight gain. *N Engl J Med* 2000; 342(12):861-867.

(66) Rintamaki R, Grimaldi S, Englund A, Haukka J, Partonen T, Reunanen A et al. Seasonal changes in mood and behavior are linked to metabolic syndrome. *PLoS ONE* 2008; 3(1):e1482.

(67) Pjrek E, Winkler D, Abramson DW, Konstantinidis A, Stastny J, Willeit M et al. Serum lipid levels in seasonal affective disorder. *Eur Arch Psychiatry Clin Neurosci* 2007; 257(4):197-202.

(68) Morgan RE, Palinkas LA, Barrett-Connor EL, Wingard DL. Plasma cholesterol and depressive symptoms in older men. *Lancet* 1993; 341(8837):75-79.

(69) Terao T, Iwata N, Kanazawa K, Takano T, Takahashi N, Hayashi T et al. Low serum cholesterol levels and depressive state in human dock visitors. *Acta Psychiatr Scand* 2000; 101(3):231-234.

(70) Nakao M, Yano E. Relationship between major depression and high serum cholesterol in Japanese men. *Tohoku J Exp Med* 2004; 204(4):273-287.

(71) Brown SL, Salive ME, Harris TB, Simonsick EM, Guralnik JM, Kohout FJ. Low cholesterol concentrations and severe depressive symptoms in elderly people. *BMJ* 1994; 308(6940):1328-1332.

(72) Glueck CJ, Tieger M, Kunkel R, Hamer T, Tracy T, Speirs J. Hypocholesterolemia and affective disorders. *Am J Med Sci* 1994; 308(4):218-225.

(73) Freedman DS, Byers T, Barrett DH, Stroup NE, Eaker E, Monroe-Blum H. Plasma lipid levels and psychologic characteristics in men. *Am J Epidemiol* 1995; 141(6):507-517.

(74) Bacon SL, Pelletier R, Lavoie KL. The impact of acute and chronic exercise on thrombosis in cardiovascular disease. *Thromb Haemost* 2009; 101(3):452-459.

(75) Goldfinger TM. Beyond the French paradox: the impact of moderate beverage alcohol and wine consumption in the prevention of cardiovascular disease. *Cardiol Clin* 2003; 21(3):449-457.

(76) Miller TD, Balady GJ, Fletcher GF. Exercise and its role in the prevention and rehabilitation of cardiovascular disease. *Ann Behav Med* 1997; 19(3):220-229.

(77) Seltzer CC. Smoking and coronary heart disease. *N Engl J Med* 1973; 288(22):1186.

(78) Mersch PP, Vastenburg NC, Meesters Y, Bouhuys AL, Beersma DG, Van Den Hoofdakker RH et al. The reliability and validity of the Seasonal Pattern Assessment Questionnaire: a comparison between patient groups. *Journal of Affective Disorders* 2004; 80(2-3):209-219.

(79) Murray G. The Seasonal Pattern Assessment Questionnaire as a measure of mood seasonality: a prospective validation study. *Psychiatry Research* 2003; 120(1):53-59.

(80) Thompson C, Stinson D, Fernandez M, Fine J, Isaacs G. A comparison of normal, bipolar and seasonal affective disorder subjects using the Seasonal Pattern Assessment Questionnaire. *Journal of Affective Disorders* 1988; 14(3):257-264.

(81) Christensen EM, Larsen JK, Gjerris A. The stability of the Seasonal Pattern Assessment Questionnaire score index over time and the validity compared to classification according to DSM-III-R. *Journal of Affective Disorders* 2003; 74(2):167-172.

(82) Booker JM, Hellekson CJ. Prevalence of seasonal affective disorder in Alaska. *American Journal of Psychiatry* 1992; 149(9):1176-1182.

(83) Rosen LN, Targum SD, Terman M, Bryant MJ, Hoffman H, Kasper SF et al. Prevalence of seasonal affective disorder at four latitudes. *Psychiatry Research* 1990; 31(2):131-144.

(84) Wehr TA, Rosenthal NE. Seasonality and affective illness. *American Journal of Psychiatry* 1989; 146(7):829-839.

(85) Lund E, Hansen V. Responses to the Seasonal Pattern Assessment Questionnaire in Different Seasons. *American Journal of Psychiatry* 2001; 158:316-318.

(86) Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica* 1983; 67(6):361-370.

(87) Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *Journal of Psychosomatic Research* 2002; 52(2):69-77.

(88) Akerstedt T, Knutsson A, Westerholm P, Theorell T, Alfredsson L, Kecklund G. Sleep disturbances, work stress and work hours: a cross-sectional study. 2002: 741-748.

(89) Harma M, Tenkanen L, Sjoblom T, Alikoski T, Heinsalmi P. Combined effects of shift work and life-style on the prevalence of insomnia, sleep deprivation and daytime sleepiness. *Scand J Work Environ Health* 1998; 24(4):300-307.

(90) Kecklund G, Akerstedt T. The psychometric properties of the Karolinska Sleep Questionnaire. *J Sleep Res* 1992; 1 (Suppl.1)(1):113.

(91) Ursin R, Bjorvatn B, Holsten F. Sleep duration, subjective sleep need, and sleep habits of 40- to 45-year-olds in the Hordaland Health Study. *Sleep* 2005; 28(10):1260-1269.

(92) Hublin C, Kaprio J, Partinen M, Koskenvuo M. Insufficient sleep-a population-based study in adults. *Sleep* 2001; 24:329-400.

(93) Reichborn-Kjennerud T. Comorbid disorders. In: Partonen T, Magnusson A, editors. Seasonal Affective Disorder. Practice and Research. New York: Oxford University Press, 2001: 19-30.

(94) Oyane N, Holsten F, Ursin R, Bjorvatn B. Seasonal variations in mood and behaviour associated with gender, annual income and education: the Hordaland Health Study. *European Journal of Epidemiology* 2005; 20(11):929-937.

(95) Parslow RA, Jorm AF, Butterworth P, Jacomb PA, Rodgers B. An examination of seasonality experienced by Australians living in a continental temperate climate zone. *Journal of Affective Disorders* 2004; 80(2-3):181-190.

(96) Hansen V, Jacobsen BK, Arnesen E. Prevalence of serious psychiatric morbidity in attenders and nonattenders to a health survey of a general population : the Tromso Health Study. *Am J Epidemiol* 2001; 154(10):891-4.

(97) Watson D, Pennebaker JW. Health complaints, stress and distress: Exploring the central role of negative affectivity. *Psychol Rev* 1989; 96:234-254.

(98) Magnusson A. An overview of epidemiological studies on seasonal affective disorder. *Acta Psychiatr Scand* 2000; 101(3):176-84.

(99) Thompson C, Thompson S, Smith R. Prevalence of seasonal affective disorder in primary care; a comparison of the seasonal health questionnaire and the seasonal pattern assessment questionnaire. *J Affect Disord* 2004; 78(3):219-226.

(100) Thompson C, Cowan A. The Seasonal Health Questionnaire: a preliminary validation of a new instrument to screen for seasonal affective disorder. *J Affect Disord* 2001; 64(1):89-98.

(101) Halle MT, Dilsaver SC. Comorbid panic disorder in patients with winter depression. *American Journal of Psychiatry* 1993; 150(7):1108-1110.

(102) Magnusson A, Partonen T. The diagnosis, symptomatology and epidemiology of seasonal affective disorder. *CNS Spectr* 2005; 10(8):625-634.

(103) Sarafidis PA, Nilsson PM. The metabolic syndrome: a glance at its history. *J Hypertens* 2006; 24(4):621-626.

(104) Lavie CJ, Milani RV. Adverse psychological and coronary risk profiles in young patients with coronary artery disease and benefits of formal cardiac rehabilitation. *Arch Intern Med* 2006; 166(17):1878-1883.

(105) Sher L. Effects of seasonal mood changes on seasonal variations in coronary heart disease: role of immune system, infection, and inflammation. *Med Hypotheses* 2001; 56(1):104-106.

(106) Laposky AD, Bass J, Kohsaka A, Turek FW. Sleep and circadian rhythms: key components in the regulation of energy metabolism. *FEBS Lett* 2008; 582(1):142-151.

(107) Patberg WR, Rasker JJ. Weather effects in rheumatoid arthritis: from controversy to consensus. A review. *J Rheumatol* 2004; 31(7):1327-1334.

(108) Storms WW. Review of exercise-induced asthma. *Med Sci Sports Exerc* 2003; 35(9):1464-1470.

(109) Conrad P. The medicalization of Society: On the transformation of Human Conditions into Treatable Disorders. Baltimore: The John Hopkins University Press, 2007.

(110) Sher L. The role of genetic factors in the etiology of seasonality and seasonal affective disorder: an avolutionary approach. *Med Hypotheses* 2000; 54(5):704-707.

(111) Avery DH, Kizer D, Bolte MA, Hellekson C. Bright light therapy of subsyndromal seasonal affective disorder in the workplace: morning vs. afternoon exposure. *Acta Psychiatr Scand* 2001; 103(4):267-274.

(112) Golden RN, Gaynes BN, Ekstrom RD, Hamer RM, Jacobsen FM, Suppes T et al. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *Am J Psychiatry* 2005; 162(4):656-662.